

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

In the Matter of)
)
MDMA SCHEDULING)

DIRECT TESTIMONY OF LEWIS S. SEIDEN, Ph.D.

1. I, Lewis S. Seiden, make the following statement:

I am a Professor in the Department of Pharmacological and Physiological Sciences at the University of Chicago and I hold joint appointments in the Department of Psychiatry and the College. I have been a faculty member at the University of Chicago since 1965. I received B.A. and B.S. degrees from the University of Chicago in 1956 and 1958, respectively and a Ph.D. in 1962 from the same Institution. I was a Postdoctoral Fellow in the Department of Pharmacology at the University of Goteborg in Sweden from 1962 to 1963 and I was a Postdoctoral Fellow at Stanford University, Department of Pharmacology from 1964 until 1965. I have been engaged as a research scientist in the fields of psychopharmacology and neuropharmacology and a copy of my curriculum vitae is attached as exhibit 1.

2. 3,4-Methylenedioxymethylamphetamine (MDMA) may be toxic to serotonin (5-hydroxytryptamine, 5HT) neurons in the human brain. If so, this would be serious because the 5HT cells are believed to play a major role in pain perception, sleep, and affect the regulation and expression of aggressive and sexual behavior.

3. In my laboratory, we have not examined MDMA effects in humans or lower animals, but based on work in 3 other species with closely related compounds, I believe that there is sufficient evidence to proceed with great caution in using this drug. The evidence which supports this conclusion is outlined below

a) First, methylamphetamine (MA, a structurally related compound; see exhibits 2 and 3), has long lasting effects on both dopamine (DA), and 5HT neurons in the central nervous system when administered in relatively high but short duration, or repeated but lower doses (exhibit 4). Following several dosing regimes, there is a decrease in steady state levels of DA and 5HT in various brain regions for weeks after discontinuation of the drug in rats (exhibit 7). DA is depleted in the striatum, the limbic system and the frontal cortex for as long as 8 weeks after the administration of MA and there is no sign of recovery. The depletion of 5HT does not seem to last as long as DA; in fact at 8 weeks, levels in some brain regions returned to near normal. However, the question remains open whether the apparent sprouting of 5HT neurons restores functionally normal synapses. And in addition to the depletion of DA and 5HT, we and others have observed a decrease in the enzymes which control the rate of synthesis of these transmitters, and a decrease in the number of their uptake sites. In vitro measurement of

kinetic constants revealed a decrease in the number of enzyme molecules and a decrease in the number of uptake sites; the affinity constants for both synthesis and uptake did not change. These results are consistent with nerve terminal degeneration. Finally, we have obtained direct anatomical evidence of nerve terminal degeneration using the Fink-Heimer staining procedures (exhibit 8).

- b. Second, amphetamine (exhibit 9) causes patterns of neurochemical change very similar to those just described for methylamphetamine (although there are slight differences in the dose required).
- c. Third, with both methylamphetamine and amphetamine, we have obtained evidence suggesting degeneration of neurons in rats, guinea pigs and rhesus monkeys (exhibit 4). Other investigators have obtained similar evidence in mice and cats. Given the consistent results among five diverse mammalian species, one would logically infer that the same damage could occur in humans.
- d. Fourth, we find methylenedioxymphetamine (MDA) is toxic to 5HT fibers in rats (exhibit 10), using both chemical and anatomical criteria. MDA has these effects at much lower doses than those required to achieve the same effects with amphetamine or methylamphetamine.
- e. MDA is chemically related to amphetamine, the major

difference being the presence of the dioxymethylene group at the 3 and 4 position of the phenyl ring. The major difference between MDMA and MDA is the presence of a methyl group on the terminal nitrogen. In our experimental work, the methyl group (i.e., MA) on amphetamine (A) did not confer any less neurotoxicity on this molecule (see above).

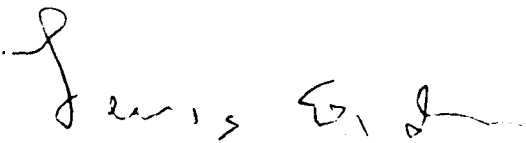
4. Therefore, I strongly suspect that MDMA will have a profile of neurotoxicity similar to that of MDA. It is true that we have not yet tested MDA in species other than rats, but again we have found that all compounds of this group so far tested show species generality. Based on the evidence available I would predict that MDA and MDMA will have the same neurotoxic effects in other mammalian species, including humans. Close chemical analogs of MDMA including MA, A, and MDA are toxic in brain, and this makes it appear extremely likely that MDMA will produce similar toxic effects. Further, as shown with MDA, the drug is toxic in the rat at doses that are very low when compared to toxic doses of MA or A. This is true regardless of whether dose is measured on a molar or an efficacy basis. This would suggest that humans taking MDA or MDMA in doses such as 100-120 mg could undergo similar toxic effects.
5. MDMA has a neurotoxic potential in humans yet to the best of my knowledge, this compound has not been systematically screened for efficacy for the treatment of mood or behavioral disorders. The evidence attesting to its efficacy

as presented for example by Dr. Richard Ingrasci, is not controlled by double blind procedures comparing placebo to MDMA. The claim that MDMA has beneficial effects is suspect because of the multiplicity of variables that are confounded with taking the drug: e.g., fasting for 4-6 hrs, couples taking the drug together, being encouraged by the therapist to talk to significant others in an intimate setting, and writing down the results of the entire experience. In addition, Dr. Ingrasci regrettably presents no systematic summary of the cases he has observed but rather presents a few anecdotal cases. These few anecdotal cases, so mixed with other treatment variables hardly make a case for the specific efficacy of this compound.

6. In a drug trial the preliminary case for efficacy must be weighed against the potential for harmful side effects. The case to date that MDMA is an effective drug seems weak; furthermore, there is evidence to suggest that the drug could harm 5HT cells in brain. As noted above, 5HT cells are believed to play a major role in pain perception, sleep, and to affect regulation and expression of aggressive and sexual behavior. It would follow from the above evidence that clinical scientists should conduct trials of MDMA in humans only with the utmost caution. They should ensure that the potential benefits to the person is great enough to outweigh the risks, and they should collect the data in a systematic and well controlled manner as is usually done under an Investigational New Drug Permit.

I declare under penalty of perjury that the foregoing statement is true and correct.

Executed on May 15, 1985

A handwritten signature in cursive script, appearing to read "Lewis S. Seiden", written above a horizontal line.

Lewis S. Seiden, Ph.D.